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FULL PAPER

An efficient two-step preparation of α-, β-, γ- or δ-aminoacids from 2-hydroxy pyrazines, pyrimidines or pyridines respectively

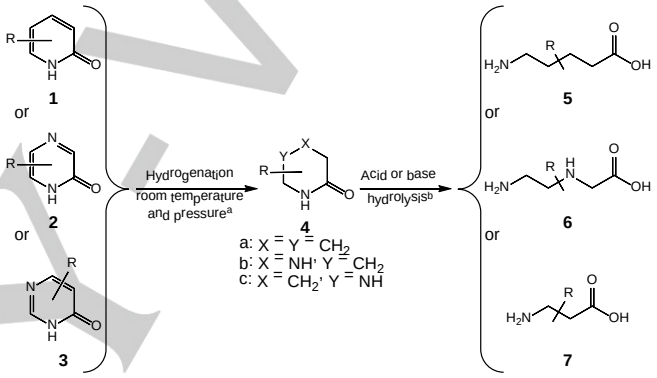
Dr. Boulos Zacharie*[a], Dr. Shaun D. Abbott[a], Christopher B. Baigent[a], Christopher Doyle[a] and Dr. Ravi Shekar Yalagala[a]

Abstract: A practical and efficient two-step procedure is reported for the preparation of a variety of α-, β-, γ- and δ-amino acids from 2-pyridone, 2-pyrazinone or 2-hydroxypyrimidine and derivatives. The procedure is amenable to scale-up and in most cases no chromatographic purification of the product is required. This approach is useful, especially in the synthesis of amino acids or deuterated amino acids that are not obtained by other methods.

Introduction

Amino acids can be classified according to the core structural functional groups' locations as alpha-(α-), beta-(β-), gamma-(γ-) or delta-(δ-) amino acids.[1] The naturally occurring amino acids have a common structure which are α-substituted derivatives. In the case of β-, γ- or δ amino acids, these are unnatural or unusual amino acids, which often contribute to special biological activity.[2,3] Synthesis of these compounds has gained significant importance because of their interesting pharmacological[4,5] and therapeutic applications.[6,7] Much progress has been made in the development of methods for their preparation. Nonetheless, new approaches in peptide synthesis are still emerging.[8] Simple processes that allow the conversion of substituted heterocycles that contain nitrogen to amino acids are very desirable. These procedures are of considerable interest, especially with regards to the synthesis of amino acid derivatives that are not obtained by other methods. Our goal, therefore, was to develop a general, simple two-step procedure for the preparation of α-, β-, γ- or δ-amino acids from functionalized heterocycles.

As part of our research, we were interested in the synthesis of piperidine derivatives because of their diverse biological activities.[9] In fact, we developed an efficient procedure for the preparation of piperidines by the reduction of pyridine *N*-oxides.[10] However, little work has been undertaken on the use of saturated and unsaturated derivatives of pyridine and pyridone as synthetic precursors to amino acids.[11] One strategy was to convert substituted 2-pyridone **1** to the corresponding 2-piperidone **4** (X = Y = CH_2) by catalytic hydrogenation, followed by acid or base hydrolysis of the resulting lactam to the δ-amino acids (i.e., substituted 5-aminovaleric acid) **5**, without use of chromatographic purification (Scheme 1). Subsequently, it would be useful to apply this approach to convert other molecules such as 2-pyrazinone (**2**) and 2-hydroxypyrimidine (**3**) derivatives to amino acid derivatives.



Scheme 1. General scheme for the preparation of α-, β- or δ-aminoacids from 2-hydroxy pyrazines, pyrimidines or pyridines respectively. [a] Typically 0.1M in MeOH; 50 wt% of 10%-Pd/C; [b] either 6M aq. HCl or KOH (12 eq.)/EtOH/H_2O reflux o/n.

Hydrogenation of heterocyclic compounds remains a challenging process despite the efforts achieved to date in this area. The major obstacle concerns the need to break the energy barrier established by aromaticity, which has generally resulted in the requirement for elevated pressures and reaction temperatures. A number of unsuccessful procedures have been described in the literature for the reduction of 2-pyridone to 2-piperidone derivatives. For example, reduction of 6-methyl-2-pyridone using ruthenium(II)-based complex bearing chiral ligands in the presence of a base potassium tert-butoxide and under a pressure of 70 bar of hydrogen at 60 °C for 24 h gave no product.[12] Only starting material was recovered. However, formation of the product occurred if an additive was added and temperature and pressure were increased significantly.[12] This procedure suffers from many drawbacks, including harsh conditions and variable yields. Another example of incomplete reduction of other 2-pyridone derivatives was the hydrogenation of 1,5-dihydroxy-2-pyridone **9** to the corresponding 2,5-piperidinedione using Pd/C in ethanol and refluxed for 24 h. This gave a mixture of the starting pyridone and the final product piperidone in a yield ratio of 28% and 14% respectively. The yield of the product was increased to 65% by adding acetic acid to the mixture but 21% of the starting material was isolated from the reaction.[13] Better yield was obtained by using Raney nickel catalyst in methanol for 24 h at room temperature followed by 6 h reflux.[13] However, the purity

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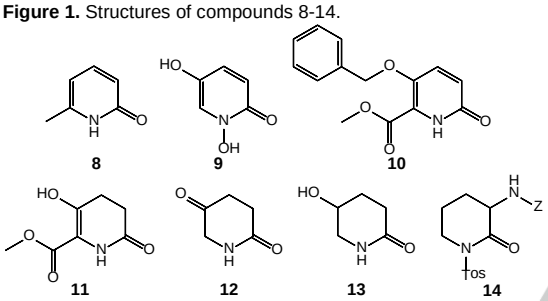
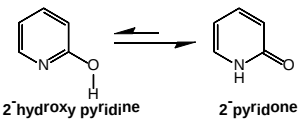
and the characterization of the crude product was not reported. Again, this method is limited to the temperature, choice of catalyst, purity and the final yield of 2,5-piperidinedione. Also, it was reported that in some cases hydrogenation of disubstituted 2-pyridone was slow. For example, reduction of methyl 3-(benzyloxy)-6-oxo-1,6-dihydropyridine-2-carboxylate **10** using palladium on charcoal proceeded very slowly at room temperature.[14] It required one week to yield 50% of the product **11**. Increasing the pressure to 10 bar and the temperature to 50 °C did not improve the yield. Replacing the Pd/C catalyst by PtO_2 gave a mixture of products including the reduction of the phenyl ring of the benzyloxy group.[14] This catalytic hydrogenation depends on the type of catalyst and is not selective. For example, other functional groups are reduced under these conditions. Similarly, hydrogenation of 5-hydroxy-2-pyridone using Pd/C at 30 °C gave a mixture of two compounds 2,5-piperidinedione **12** and 5-hydroxypiperidone **13**.[15] Therefore, there is still a need for a facile method for the reduction of 2-pyridone derivatives by selection of the appropriate catalyst or choice of the best reaction conditions.

Figure 1. Structures of compounds 8-14.



Few methods are reported for the conversion of different heterocycles including 2-piperidone to amino acids.[16] For example, acid hydrolysis of 2,5-piperidinedione **12** gave only 51% yield of 5-amino-4-oxopentanoic acid.[15] In addition, few *N*-substituted-2-piperidone derivatives have been used for amino acid synthesis.[11] For example, ammonolysis of 1-tosyl-3-L-benzyloxycarbonylamino-2-piperidone **14** for 2 days followed by hydrogen bromide/acetic acid for 5 days afforded the desired product *N*-2-benzoyloxycarbonyl-N-5-tosyl-L-ornithine amide.[11b] This procedure has many drawbacks including the multi-step preparation of the starting 2-piperidone **14**, lengthy reaction time, difficult deprotection of the N^{δ}-tosyl group and the purification of the final product ornithine amide. Furthermore, acid or alkaline hydrolysis of 1-benzyl-2-piperidone substituted at position 4- or 5- tends to reach an equilibrium between the starting 2-piperidone and ring-opened derivatives which affects the yield of hydrolysis.[11c] Another example containing 2-piperidone skeleton and which serves as precursors to amino acids is dihydrouracil. Acid hydrolysis of 6-substituted dihydrouracils at 160 °C led to cleavage of the ring and formation of β-aminopropionic acid derivatives in low yield with unsaturated compounds as the main products.[17] Although under basic condition the reaction gave the desired product, the amino acids obtained were not pure (have uncorrected melting points).[17] All of these procedures are limited to multi-step synthesis, high reaction temperature, harsh conditions, the purity of the final product, the availability and the selection of appropriate catalyst for the preparation of starting intermediates. In general, these reactions are not amenable for scale-up and gave variable yields. Therefore, there is still a need for the development of a general and easy method for the preparation of amino acids from saturated heterocycle-2-one derivatives.

2-Pyridone (**1**) exhibits iminol-amide tautomerism.[18] In polar media the pyridone form is favored (Scheme 2); the tautomeric equilibrium shifts to the hydroxypyridine form as solvent polarity decreases. In the reduction step, we used methanol as a solvent to favor the pyridone form. Also, the electronic effect of substituents at the 2-pyridone ring may influence the position of the tautomeric equilibrium.[18] Protecting the nitrogen atom of 2-pyridone can shift the tautomeric equilibrium toward the lactam form.[11c] When 2-pyridone is subjected to catalytic reduction, the resultant product is a cyclic amide. Of all the groups amenable to catalytic hydrogenation, the amide is the most difficult to reduce. In general, 2-piperidone behaves as an aminoketone.[19] Furthermore, the nitrogen atom of 2-pyridone or piperidone should not be basic enough to cause catalyst poisoning. Because the absence of the tautomerism in 3-hydroxypyridine, this compound is not hydrogenated under mild conditions. In addition, the unprotected nitrogen atom of the 3-derivative inhibits the activity of the catalyst.[19]



Scheme 2. Iminol-amide tautomerism of 2-pyridone.

Results and Discussion

Our results are summarized in Table 1. A variety of 2-pyridones (entries 1-15), 2-quinolones (entry 16) and 3-hydroxyisoquinolines (entry 17) are reduced efficiently to their piperidone derivatives. Also, 2-pyrazinones (entries 18 and 19) and 2-hydroxypyrimidines (entries 20 and 21) are converted in high yield to their reduced form 2-oxopiperazine and tetrahydro-2-pyrimidone respectively. The reaction is carried out using palladium on carbon in methanolic solution overnight at room temperature. Adding a weak acid, such as acetic acid, did not affect the yield. Changing the solvent methanol for other solvents did however alter the yield. For entry 1, reduction under the standard condition in different solvents such as 2-butanone, tetrahydrofuran, acetone, or dimethylformamide gave low yield of the product. Also, other reducing systems appear to be inefficient under this type of reduction conditions, for example, ammonium formate/Pd on carbon and Wilkinson's catalyst/hydrogen. In contrast, hydrogenation in the presence of Raney nickel gave similar result compared to palladium on carbon.

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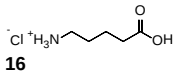
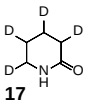
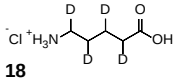
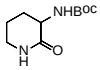
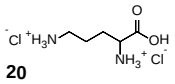
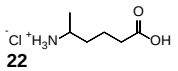
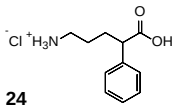
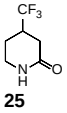
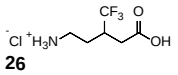
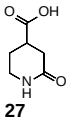
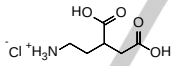
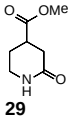
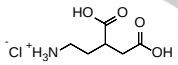
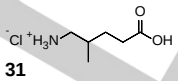
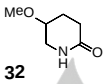
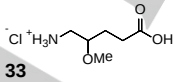
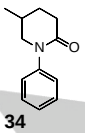
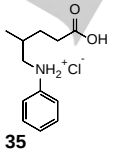
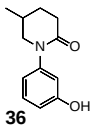
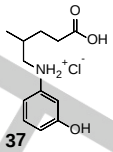
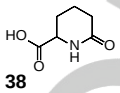
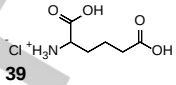
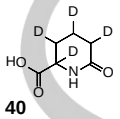
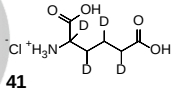
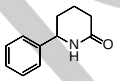
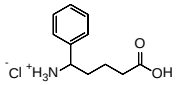
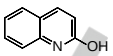
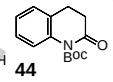
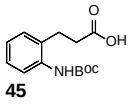
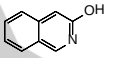
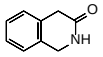
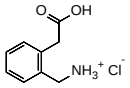
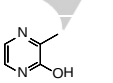
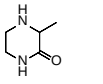
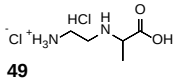
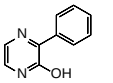
Table 1. Reduction and ring opening products of 2-pyridone, 2-hydroxypyrazine, 2-pyrimidone and derivatives.

Entry	SM*	Reduction product	Yield (%)	Hydrolysis product	Yield (%)
1	H	 **15**	92	 **16**	98
2	H	 **17**	96	 **18**	85
3	3-NHBoc	 **19**	60	 **20**	84
4	6-CH_3	 **21**	95	 **22**	71[d]
5	3-C_6H_5	 **23**	99	 **24**	95
6	4-CF_3	 **25**	96	 **26**	83
7	4-COOH	 **27**	100	 **28**	71
8	4-$COOCH_3$	 **29**	94	 **28**	[e]
9	5-CH_3	 **30**	99	 **31**	98
10	5-OCH_3	 **32**	98	 **33**	81
11	1-phenyl-5-CH_3	 **34**	92	 **35**	87
12	1-(3-hydroxyphenyl)-5-CH_3	 **36**	89	 **37**	55
13	6-COOH	 **38**	90	 **39**	93[f],52[g]
14	6-COOH	 **40**	100	 **41**	87
15	6-phenyl	 **42**	86	 **43**	[h]
16		 **44**	90[j]	 **45**	98[j]
17		 **46**	95	 **47**	89[f],82[g]
18		 **48**	100	 **49**	98
19		**50**	99	**51**	94
20		**52**	91	**53**	97
21		**54**	96	**55**	99
22		**56**	42	**57**	65

* for entries 1-15; SM structure for entries 16-22.

[a] 2-Pyridones, 2-hydroxypyrazines and pyrimidines are commercially available or are simply prepared according to the literature procedure. [b] All products had spectroscopic characteristics consistent with the assigned structures. [c] Isolated yield. [d] Hydrogenation was performed using PtO_2. [e] Similar to entry 28. [f] Ring opening under acidic conditions (HCl). [g] Ring opening under basic conditions (KOH) followed by purification using acidic ion-exchange. [h] Observed in a crude but lost on purification. [i] Ring opening under basic conditions (LiOH). [j] Yield for reduction step; which was then followed by Boc-protection.

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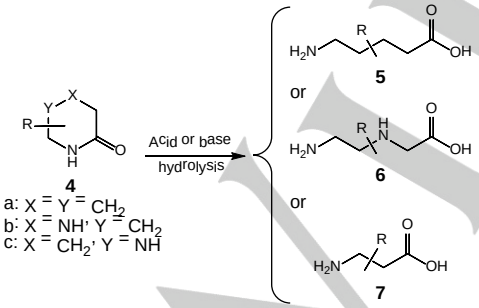
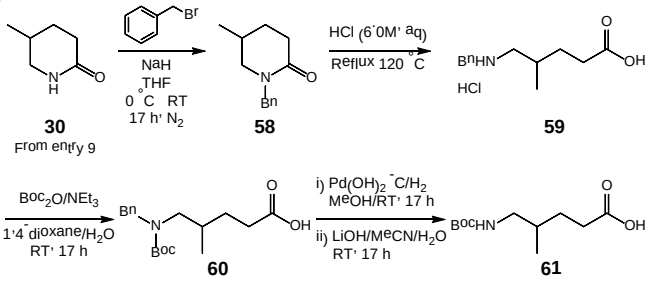
The reaction conditions are very mild. As a result, several reducible functionalities such as methoxycarbonyl (entry 8), carboxyl (entries 7, 13 and 14), or methoxy (entry 10) are unaffected with this reagent system. However, fluorine[20] or chlorine atoms in the 3 or 5 position respectively are readily eliminated under the standard reaction conditions. In the case of 3-nitro, reduction of this function to the corresponding amino group is the only product observed in the reaction mixture. Therefore, protection of the 3-amino group with a Boc group followed by hydrogenation on Pd/C gave 3-Boc-amino-2-piperidone in reasonable yield (entry 3). We hypothesized that the 3-amino group poisoned the catalyst and subsequently prevented reduction of 2-pyridone. Another example where hydrogenation of substituted 2-pyridone using Pd/C gave low yield is the reduction of 6-methyl-2-pyridone **8**. This compound was reported in the literature[12] to be very difficult to reduce using ruthenium(II) as a catalyst, in the presence of a base, high pressure of hydrogen and a temperature of 60 °C for 24 h. However, changing the palladium or ruthenium(II) catalysts to the more active Adams' catalyst PtO_2 afforded the desired product 6-methyl-piperidin-2-one in 95% yield (entry 4). Also, it was observed that reduction of 4-hydroxymethylpyridin-2-one with Pd/C gave only 4-methylpiperidone in high yield.[20] Similar results were obtained by reacting 1-benzyl-5-(hydroxymethyl)pyridine-2-one with Pd/barium sulfate in methanol and under high pressure of hydrogen. The C-O cleaved product is isolated in 71% yield.[21] Our procedure is simple, general and does not require special apparatus, or harsh conditions. The workup is easy, requiring only filtration of catalyst followed by removal of the solvent. The yield of the crude product is >86%. No purification is required, and the crude product is pure (>98%) and is used in the next step without further purification.

Following the reduction of 2-pyridone, ring opening of the lactams **4** was investigated (Scheme 3). This gave α-amino acids [entries 3 (ornithine), 13 (2-aminoadipic), 14 (deuterated 2-aminoadipic), 18 (N-aminoethylalanine), 19 (N-aminoethyl-α-phenylglycine)], β-amino acid derivatives (entry 20 and 21), γ-amino acid (4-aminobutyric derivatives) (entry 7) and δ-amino acids (5-aminovaleric acid derivatives) (entries 1, 2, 4-17) in good yield.



Scheme 3. General scheme for the preparation of α-, β- or δ-aminoacids from 2-hydroxy pyrazines, pyrimidines or pyridines respectively.

Two approaches were examined for the cleavage of lactam **4** to the corresponding amino acids **5**, **6** and **7**. Acid hydrolysis using aqueous 6M hydrochloric acid, or alkaline hydrolysis using potassium or lithium hydroxide. In case of the acidic conditions, pure product was obtained in a good yield. In comparison, alkaline hydrolysis gave high yield, but less pure product. Therefore, a quick purification using anion exchange resin was employed, in order to obtain high purity amino acids for commercial purpose. In the case of 3,4-dihydro-2(1*H*)-quinolinone (entry 16 without the Boc group), no ring opening was observed using acidic or basic conditions. In contrast, alkaline hydrolysis of *N*-Boc-protected 2-quinolinone resulted in the formation of 4-(2-Boc-aminophenyl) propionic acid in high yield (entry 16). This indicated that protecting the nitrogen atom of dihydroquinolin-2-one is necessary to shift the tautomeric equilibrium toward the lactam form.[11c,22] In general, *N*-substituted 2-pyridone or derivatives were more easily hydrogenated[14] and cleaved[22] to the corresponding substituted amino acids than the unprotected substrate. Good examples of high yield *N*-protected piperidin-2-one product is the reduction of *N*-phenyl or *N*-(3-hydroxyphenyl)-5-methyl-pyridin-2-one (entries 11 and 12 respectively). We applied this approach to develop a general procedure for the preparation of Boc or Z-amino acids. However, it is reported that the preparation of *N*-Boc, *N*-CBZ or *N*-acetylpyridin-2-one gave inseparable mixture of O- and *N*-substituted isomers compared to the selective formation of the corresponding *N*-alkyl or *N*-aryl derivatives. In fact, preparation of *N*-Boc-pyridin-2-one in good yield required harsh conditions such as n-butyl lithium and DABCO.[9c] To avoid these reagents, we developed a general route for the preparation and scale-up of *N*-Boc amino acids (Scheme 4). Reduction of 5-methylpyridin-2-one under our conditions gave the corresponding piperidone **30**, which was benzylated to afford *N*-benzyl derivative **58** in 67% yield. Opening of the ring under acidic conditions gave the corresponding amino acid **59**, which was converted to the Boc derivative **60** in 79% yield (over 2 steps) using the standard procedure. Hydrogenolysis of the benzyl group in methanol, followed by hydrolysis of any ester formed, gave the expected Boc amino acid **61** in 62% yield.



Scheme 4. Preparation of 5-*N*-Boc amino-3-methylvaleric acid from 5-methyl-2-piperidone.

Deuterated drugs are widely used in studies of metabolism of drugs and toxic substances in humans and animals.[23] The generality of our synthesis was investigated by the preparation of deuterated 2-piperidone,[24] oxopiperazine or dihydro-2-pyrimidone derivatives which are converted to α-, β-, γ- or δ-deuterated amino acids. For example, treating 2-pyridone or 2-hydroxypyridine-6-carboxylic acid with D2/Pd-C in methanol gave the corresponding [2H]4-labelled compounds (entries 2 and 14).

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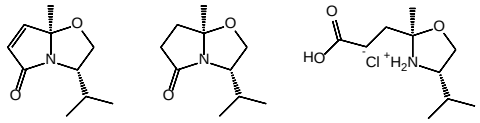
Hydrolysis of these compounds afforded deuterated 5-aminovaleric acid (entry 2) and aminoadipic acid (entry 14) in high yield and up to 99% d4-deuteration respectively. These deuterated compounds may find use in those applications that require enriched isotopic labels such as metabolic studies. They are obtained in good yield, high isotopic content, and at minimum cost.

Encouraged by these results, this methodology was applied to more complex molecules. For example, reduction of chiral bicyclic lactam **62** using Pd/hydrogen in ethyl acetate gave the expected reduced product **56** (entry 22) which was hydrolyzed to the corresponding chiral amino acid **57** (entry 22).

Figure 2. Structures of compounds 56, 57 and 62.



62 **56** **57**

Conclusions

In conclusion, a practical and efficient two-step procedure for the preparation of a variety of α, β-, γ- and δ-amino acids from 2-pyridone, 2-pyrazinone or 2-hydroxypyrimidine and derivatives is reported herein. The first reaction is the reduction of these compounds using hydrogen and a metal catalyst such as palladium on carbon, or platinum oxide or Raney nickel followed by acid or base hydrolysis to give the expected amino acids in high yield. The procedure is amenable to scale-up and in most cases no chromatographic purification of the product is required. This approach is of considerable interest, especially in the synthesis of amino acids or deuterated amino acids that are not obtained by other methods. Because of the growing interest in the enantiopure synthesis of aliphatic cyclic compounds, the first step is expected to be applicable to synthesize stereoselective piperidin-2-one and derivatives using appropriate chiral catalyst.[20]

Experimental Section

General Information

All reagents and catalysts were purchased from commercial sources (Sigma-Aldrich, TCI) and used without any further purification. ^{1}H and ^{13}C NMR were recorded on a Varian 400 MHz spectrometer using $CDCl_3$ or CD_3OD as NMR solvents. Mass spectra were recorded on an Acquity H-Class, QDA detector, PDA eλ detector. MS-MS mass spectra were recorded on a TSQ Quantum Access MAX and analysed by positive electrospray ionization.

Typical procedure for the reduction of 2-pyridone, 2-hydroxypyrazine, 2-pyrimidone and derivatives

A solution of the 2-pyridone 2-hydroxypyrazine or 2-pyrimidone derivative (1 mmol) in methanol (10 mL) was treated with 10 %-Pd/C (50-100 wt%) and then the reaction mixture was saturated with hydrogen gas (two cycles). The solution was then stirred at room temperature under hydrogen atmosphere for 24 h. The reaction was filtered through celite and washed with methanol (2 x 10 mL). Evaporation of the solvent afforded the expected reduced product in high yield. This compound was used in the next step without further purification.

Typical procedure for ring-opening in acidic condition of 2-piperidone, 2-oxopiperazine, and tetrahydro-2-pyrimidone derivatives

A mixture of 2-piperidinone derivative (1 mmol) and 6M aqueous hydrochloric acid (10 mL), was stirred at 90 °C for 24 h. Evaporation of the solvent under reduced pressure followed by complete dryness of the compound under high vacuum for 24 h gave the expected ring-opened product.

Typical procedure for ring-opening in basic condition of 2-piperidone, 2-oxopiperazine, and tetrahydro-2-pyrimidone derivatives

A solution of 2-piperidinone derivative (1 mmol) in ethanol (3 mL), was treated with a solution of potassium hydroxide (0.66 g, 11.7 mmol) in water (2 mL), and the mixture was heated at 110 °C, under reflux conditions, for 17 h. The reaction mixture was cooled to ambient temperature, then evaporated at 45 °C under reduced pressure to give a mixture of the crude product and inorganic salts. Dowex® IX2 anion exchange resin (0.7 meq/wet mL; 14 mL; 9.8 meq) was prepared by washing consecutively with 14 mL portions of 1M aq. HCl (x 1), water (x 5), 1M aq. NaOH (x 1), and water (x 5). The resin was incubated with a solution of the intermediate salt in water (10 mL), at ambient temperature for 20 min, then filtered under reduced pressure, and the filtrate (unbound fraction) set aside. The resin was eluted with 14 mL portions of water (x 5), then 0.1M aq. HCl (x 5). Product-containing fractions were degassed to remove excess HCl, then lyophilised to give the expected ring-opened product.

A second cycle of purification using the unbound fraction was carried out to yield a second portion of the desired product.

Typical procedure for ring-opening of Boc-protected 2-piperidone, 2-oxopiperazine, and tetrahydro-2-pyrimidone derivatives

The Boc-protected compound (1 mmol) is dissolved in THF (5 mL) and H_2O (2 mL) at room temperature, and LiOH (3 mmol) is added. The reaction is then left to stir at room temperature for 5 h. The reaction mixture is then diluted with 0.1 M HCl solution and extracted 3x with EtOAc. The organic layers are combined, washed with brine and dried over Na_2SO_4, and concentrated under reduced pressure, to give the desired ring-opened product.

Compound 17: 3,4,5,6-[$^{2}H]_4$-Piperidin-2-one

Translucent white solid, 523 mg (96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (br s, 1H), 2.97-3.02 (m, 1H), 2.00-2.05 (m, 1H), 1.41-1.52 (m, 2H); ^{2}H NMR (400 MHz, CH_2Cl_2 + $CDCl_3$ reference): δ 2.94 (s, 1D), 1.97 (s, 1D), 1.36-1.50 (m, 2D); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 41.0-41.6 (m), 30.5-31.0 (m), 21.2-21.8 (m) & 19.8-20.4 (m); MS-MS 104.16 (100%, MH+); HRMS (ESI-TOF) m/z MH+ Calcd for $C_5H_5D_4NO$ 104.1008, found 104.1008.

Compound 18: 2,3,4,5-[2H]4-5-Aminopentanoic acid, hydrochloride

White solid, 269 mg (85%). ^{1}H NMR (400 MHz, D_2O + CH_3CN reference): δ 7.50 (br s, signal exchanging with time), 2.98 (d, *J* = 7.8 Hz, 1H), 2.42 (dd, *J* = 7.5, 6.6 Hz, 1H), 1.59-1.70 (m, 2H); ^{2}H NMR (400 MHz, H_2O/D_2O + d6-acetone reference): δ 7.47 (br s, signal exchanging with time), 3.07 (s, 1D), 2.46 (s, 1D), 1.63-1.80 (m, 2D); ^{13}C NMR (101 MHz, D_2O + CH_3CN reference): δ 178.2, 38.9-39.4 (m), 32.8-33.3 (m), 25.6-26.2 (m) & 20.7-21.2 (m); MS-MS 122.14 (100%, free base MH+); HRMS (ESI-TOF) m/z MH+ Calcd for $C_5H_7D_4NO_2$ 122.1140, found 122.1120.

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Compound 28: (*RS*)-2-[2-Aminoethyl]butandioic acid, hydrochloride
Viscous, colourless oil, 272 mg (71%). ^{1}H NMR (400 MHz, CD_3OD): δ 2.97-3.09 (m, 2H), 2.83-2.91 (m, 1H), 2.71 (A of ABX, *J* = 17.2, 7.8 Hz, 1H), 2.56 (B of ABX, *J* = 16.8, 5.8 Hz, 1H), 1.99-2.08 (m, 1H), 1.84-1.93 (m, 1H); ^{13}C NMR (101 MHz, CD_3OD): δ 175.6, 173.6, 38.4, 37.6, 35.2 & 28.8; MS-MS 162.02 (30%, free base MH+); HRMS (ESI-TOF) m/z MH+ Calcd for $C_6H_{11}NO_4$ 162.0761, found 162.0758.

Compound 32: (*RS*)-5-Methoxypiperidin-2-one
Viscous, colourless oil, 252 mg (98%). ^{1}H NMR (400 MHz, CD_3OD): δ 3.64-3.68 (m, 1H), 3.37 (s, 3H), 3.34-3.40 (m, 2H), 2.41 (ddd, *J* = 17.6, 10.5, 6.6 Hz, 1H), 2.25 (ddd, *J* = 17.9, 6.2, 4.3 Hz, 1H), 1.99-2.05 (m, 1H), 1.90-1.96 (m, 1H); ^{13}C NMR (101 MHz, CD_3OD): δ 173.2, 71.3, 54.9, 44.8, 26.3 & 24.0; MS-MS 130.07 (100%, MH+); HRMS (ESI-TOF) m/z MH+ Calcd for $C_6H_{11}NO_2$ 130.0863, found 130.0867.

Compound 35: (*RS*)-4-Methyl-5-(phenylamino)pentanoic acid, hydrochloride
Viscous oil, 168 mg (87%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.21 (dd, *J* = 8.6, 7.4 Hz, 2H), 6.56-6.61 (m, 3H), 2.99 (A of ABX, *J* = 12.5, 5.9 Hz, 1H), 2.85 (B of ABX, *J* = 12.5, 6.6 Hz, 1H), 2.25-2.41 (m, 2H), 1.72-1.83 (m, 2H), 1.40-1.49 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 176.5, 148.9, 128.6, 116.3, 112.5, 49.7, 32.1, 31.3, 29.5 & 16.6; MS-MS 208.01 (83%, free base MH+); UPLC (1-100%-2 min): 0.96 min; HRMS (ESI-TOF) m/z MH+ Calcd for $C_{12}H_{17}NO_2$ 208.1332, found 208.1340.

Compound 36: (*RS*)-1-[3-hydroxyphenyl]-5-methylpiperidin-2-one
White solid, 181 mg (89%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.21 (dd, *J* = 8.3, 7.8 Hz, 1H), 6.67-6.73 (m, 2H), 6.66 (dd, *J* = 2.4, 1.9 Hz, 1H), 3.53-3.57 (m, 1H), 3.29-3.34 (m, 1H), 2.51 (dd, *J* = 8.4, 4.5 Hz, 2H), 2.09-2.18 (m, 1H), 1.92-1.97 (m, 1H), 1.56-1.67 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 171.1, 158.0, 144.0, 129.6, 116.9, 113.9, 113.2, 58.4, 31.3, 28.9, 28.7 & 17.1; LRMS: 206.2 (100%, MH+); MS-MS 206.03 (100%, MH+); UPLC (1-100%-5 min): 1.84 min; HRMS (ESI-TOF) m/z MH+ Calcd for $C_{12}H_{15}NO_2$ 206.1176, found 206.1185.

Compound 37: (*RS*)-4-Methyl-5-([3-hydroxyphenyl]amino)pentanoic acid, hydrochloride
Black solid, 102 mg (55%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.21 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.10-6.18 (m, 3H), 3.53-3.57 (m, 1H), 2.98 (A of ABX, *J* = 12.7, 6.1 Hz, 1H), 2.85 (B of ABX, *J* = 12.7, 6.8 Hz, 1H), 2.26-2.40 (m, 2H), 1.74-1.83 (m, 2H), 1.39-1.49 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 176.5, 157.8, 149.6, 129.4, 105.2, 104.2, 99.7, 50.2, 32.0, 31.2, 29.5 & 16.5; MS-MS 224.05 (6%, free base MH+); HRMS (ESI-TOF) no molecular ion observed.

Compound 40: 2,3,4,5-[^{2}H]$_4$-(RS)-6-oxopiperidine-2-carboxylic acid
White solid, 535 mg (quantitative). ^{1}H NMR (400 MHz, CD_3OD): δ 2.27-2.32 (m, 1H), 1.86-1.91 (m, 1H), 1.74-1.81 (m, 1H); ^{2}H NMR (400 MHz, CH_2Cl_2 + $CDCl_3$ reference): δ 4.19 (s, 1D), 2.43 (s, 1D), 2.25 (s, 1D), 1.95 (s, 1D); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 173.4, 53.5-54.1 (m), 29.6-30.1 (m), 24.1-24.6 (m) & 17.7-18.2 (m); MS-MS 148.10 (100%, MH+); HRMS (ESI-TOF) m/z MH+ Calcd for $C_6H_5D_4NO_3$ 148.0906, found 148.0914.

Compound 41: (*RS*)-2,3,4,5-[^{2}H]$_4$-2-Aminohexandioic acid, hydrochloride
Beige-coloured foam, 351 mg (87%). ^{1}H NMR (400 MHz, D_2O + CH_3CN reference): δ 2.44-2.47 (m, 1H), 1.89-2.00 (m, 1H), 1.66-1.76 (m, 1H); ^{2}H NMR (400 MHz, H_2O + CD_3OD reference): δ 4.10 (s, 1D), 2.48 (s, 1D), 1.58-2.14 (m, 2D); ^{13}C NMR (101 MHz, D_2O + CH_3CN reference): δ 178.2, 172.6, 53.0-53.4 (m), 33.2-33.6 (m), 29.3-29.6 (m) & 20.0-20.5 (m); MS-MS 166.06 (100%, free base MH+); HRMS (ESI-TOF) m/z MH+ Calcd for $C_6H_7D_4NO_4$ 166.1012, found 166.1015.

Compound 52: (*RS*)- 6-(trifluoromethyl)tetrahydropyrimidin-4(1*H*)-one
White solid, 372 mg (91%). ^{1}H NMR (400 MHz, CD_3OD): δ 4.23 & 4.18 (ABq, *J* = 12.4 Hz, 2H), 3.70-3.79 (m, 1H), 2.50 (A of ABX, *J* = 17.2, 5.5 Hz, 1H), 2.39 (B of ABX, *J* = 17.2, 10.5 Hz, 1H); ^{19}F NMR (377 MHz, CD_3OD): δ -79.06 (d, JHF = 7.9 Hz, 3F); ^{13}C NMR (101 MHz, CD_3OD): δ 169.5, 125.3 (q, JCF = 279.1 Hz), 55.9, 53.3 (q, JCF = 30.7 Hz) & 30.1; HRMS (ESI-TOF) m/z MH+ Calcd for $C_5H_7F_3N_2O$ 169.0595, found 169.0583.

Compound 57: 3-[(2*R*,4*S*)-4-Isopropyl-2-methyloxazolidin-2-yl]propanoic acid, hydrochloride
Pale yellow crystals, for a total yield of 422 mg (65%). ^{1}H NMR (400 MHz, D_2O + CH_3CN reference): δ 3.86 (A of ABX, *J* = 12.5, 3.9 Hz, 1H), 3.66 (B of ABX, *J* = 12.5, 7.8 Hz, 1H), 3.08-3.14 (m, 1H), 2.85 (t, *J* = 6.5 Hz, 2H), 2.58 (t, *J* = 6.1 Hz, 2H), 2.21 (s, 3H), 1.90-2.02 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.98 (d, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, D_2O + CH_3CN reference): δ 175.0, 119.5, 60.0, 59.0, 28.2, 28.1, 27.8, 18.3 & 18.2; MS-MS 202.06 (100%, free base MH+); HRMS (ESI-TOF) *m/z* MH+ Calcd for $C_{10}H_{19}NO_3$ 202.1436, found 202.1438.

Compound 58: (RS)-1-Benzyl-5-methylpiperidin-2-one
A suspension of sodium hydride (60% w/w, 120 mg, 2.99 mmol) in anhydrous THF (4 mL), at 0 °C, under nitrogen, was treated dropwise with a solution of (RS)-5-methylpiperidin-2-one (30 mg, 2.65 mmol) in anhydrous THF (4 mL). The reaction was then allowed to warm to ambient temperature and was stirred for 2 h. Benzyl bromide (0.34 mL, 2.84 mmol) was then added, and the reaction was stirred at ambient temperature, under argon, overnight. The reaction was quenched by addition of water (30 mL); and the mixture was extracted with a 1:1 mixture of Et_2O and EtOAc (4 x 30 mL). Combined organic extracts were washed with saturated aqueous NaCl solution; dried over Na_2SO_4; filtered and evaporated to give the crude product. Purification by chromatography on silica gel (eluting with 0 to 70% ethyl acetate in hexanes) gave the title compound (362 mg 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.34 (m, 5 H), 4.49 & 4.67 (ABq, *J* = 14.6 Hz, 2H), 3.16 (ddd, *J* = 12.1, 5.1, 2.0 Hz, 1H), 2.82 (dd, *J* = 12.1, 10.2 Hz, 1H), 2.54 (ddd, *J* = 17.9, 5.9, 3.1 Hz, 1H), 2.44 (ddd, *J* = 17.9, 11.5, 6.4 Hz, 1H), 1.80-1.96 (m, 2H), 1.41-1.52 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H).

Compound 59: (*RS*)-5-(Benzylamino)-4-methylpentanoic acid, hydrochloride
Ring-opening of (*RS*)-1-benzyl-5-methylpiperidin-2-one using the Typical Procedure for Ring-Opening in Acidic Conditions, gave the title compound as a white solid, which was used directly in the next step. ^{1}H NMR (400 MHz, D_2O): δ 7.31 (s, 5 H), 4.07 (s, 2H), 2.84 (A of ABX, *J* = 12.7, 6.1 Hz, 1H), 2.72 (B of ABX, *J* = 12.7, 8.0 Hz, 1H), 2.15-2.31 (m, 2H), 1.70-1.80 (m, 1H), 1.48-1.56 (m, 1H), 1.26-1.35 (m, 1H), 0.73 (d, *J* = 6.6 Hz, 3H).

Compound 60: (*RS*)-5-(Benzyl(tert-butoxycarbonyl)amino)-4-methylpentanoic acid
A mixture of (*RS*)-5-(benzylamino)-4-methylpentanoic acid, hydrochloride (2.27 mmol), Boc anhydride (991 mg, 4.54 mmol) and triethylamine (0.63 mL, 4.5 mmol) in 1,4-dioxane (6 mL) and water (6 mL) was stirred at ambient temperature overnight. 1,4-Dioxane was removed under reduced pressure, and the mixture was acidified by addition of 0.1M aq. HCl (50 mL), then extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with sat. aq. NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude compound. Purification by silica gel chromatography (eluting with 0-100% EtOAc in hexanes) gave the title compound (579 mg, 79% over 2 steps). ^{1}H NMR

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(400 MHz, $CDCl_3$): δ 10.5 (br s, 1H), 7.16-7.32 (m, 5 H), 4.40 & 4.46 (2 x s, cis & trans carbamates, 2H), 2.88-3.17 (m, 2H), 2.21-2.44 (m, 2H), 2.15-2.31 (m, 2H), 1.62-1.74 & 1.76-1.87 (2 x m, cis & trans carbamates, 2H), 1.34-1.45 (m, 1H), 1.41 & 1.48 (2 x s, cis & trans carbamates, 9H), 0.86 (d, *J* = 7.2 Hz, 3H) ; HRMS (ESI-TOF) m/z MH+ Calcd for $C_{18}H_{27}NO_4$ 322.2013, found 322.2018.

Compound 60: (*RS*)-5 (tert-Butoxycarbonylamino)-4-methylpentanoic acid

A solution of (*RS*)-5-(benzyl(tert-butoxycarbonyl)amino)-4-methylpentanoic acid (579 mg, 1.80 mmol) in MeOH (8 mL) was purged with nitrogen, then treated with $Pd(OH)_2$ on carbon (128 mg), placed under a hydrogen atmosphere, and stirred at ambient temperature overnight. The reaction mixture was filtered through celite, and solvent was removed under reduced pressure to give a mixture of the title compound and its methyl ester. A solution of this mixture in MeCN (24 mL) was treated with a solution of LiOH (271 mg, 11.4 mmol) in water (6 mL), and the mixture was stirred at ambient temperature overnight. The reaction was quenched by addition of 1M aq. HCl (75 mL), then extracted with EtOAc (75 mL). The organic extract was washed with sat. aq. NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give the title compound (337 mg, 62%). NMR showed signals for cis and trans carbamates. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.2 (br s, 1H), 6.28 & 4.80 (2 x s, cis & trans carbamates, 1 H), 2.81-3.01 (m, 2H), 2.23-2.39 (m, 2H), 1.53-1.71 (m, 2H), 1.37 & 1.40 (2 x s, cis & trans carbamates, 9H), 1.33-1.42 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4 & 178.3 (cis & trans carbamates), 158.0 & 156.3 (cis & trans carbamates), 80.6 & 79.2 (cis & trans carbamates), 47.1 & 46.0 (cis & trans carbamates), 33.2 & 33.1 (cis & trans carbamates), 31.5, 28.9 & 28.3 (cis & trans carbamates) & 17.1; LRMS (negative): 230.3 (100%, M - H+); UPLC (1-100%-5 min; ELSD): 2.13 min.

Registry numbers (supplied by author)

Entry 15, piperidin-2-one, 675-20-7; **entry 16**, 5-aminopentanoic acid hydrochloride, 627-95-2; **entry 19**, (*RS*)-3-(tert-butoxycarbonylamino)piperidin-2-one, 99780-98-0; **entry 20**, (*RS*)-ornithine dihydrochloride, 15160-12-0; **entry 21**, (*RS*)-6-methylpiperidin-2-one, 4775-98-8; **entry 22**, (*RS*)-5-aminohexanoic acid hydrochloride, 855913-65-4; **entry 23**, (*RS*)-3-phenylpiperidin-2-one, 51551-56-5; **entry 24**, (*RS*)-5-amino-2-phenylpentanoic acid hydrochloride, 15032-58-3; **entry 25**, (*RS*)-4-(trifluoromethyl)-piperidin-2-one, 1803588-50-2; **entry 26**, (*RS*)-5-amino-3-(trifluoromethyl)pentanoic acid hydrochloride, 1803565-62-9; **entry 27**, (*RS*)-2-oxopiperidine-4-carboxylic acid, 24537-50-6; **entry 29**, methyl (*RS*)-2-oxopiperidine-4-carboxylate, 25504-47-6; **entry 30**, (*RS*)-5-methylpiperidin-2-one, 3298-16-6; **entry 31**, (*RS*)-3-(aminomethyl)butanoic acid hydrochloride, 1423024-55-8; **entry 33**, (*RS*)-5-amino-4-methoxypentanoic acid, 1822564-26-0; **entry 34**, (*RS*)-5-methyl-1-phenylpiperidin-2-one, 1421430-33-2; **entry 38**, (*RS*)-6-oxopiperidine-2-carboxylic acid, 3770-22-7; **entry 39**, (*RS*)-2-aminohexanedioic acid hydrochloride, 67744-11-0; **entry 42**, (*RS*)-6-phenylpiperidin-2-one, 41419-25-4; **entry 44**, 1-(tert-butoxycarbonyl)-3,4-dihydroquinolin-2(1H)-one, 194979-77-6; **entry 45**, 3-[2-(tert-butoxycarbonylamino)phenyl]propanoic acid, 1070955-54-2; **entry 46**, 1,2-dihydroisoquinolin-3(4H)-one, 24331-94-0; **entry 47**, 2-[2-(aminomethyl)phenyl]acetic acid hydrochloride, 42288-55-1; **entry 48**, (*RS*)-3-methylpiperazin-2-one, 23936-11-0; **entry 49**, (*RS*)-2-[2-aminoethylamino]propanoic acid dihydrochloride; 143192-22-7; **entry 50**, (*RS*)-3-phenylpiperazin-2-one, 5368-28-5; **entry 51**, (*RS*)-2-[2-aminoethylamino]-2-phenylacetic acid dihydrochloride; 97536-15-7; **entry 53**, (*RS*)-3-amino-4,4,4-trifluorobutanoic acid hydrochloride, 91291-66-6; **entry 54**, (*RS*)-5-methyltetrahydropyrimidin-4(1H)-one, 1936491-13-2; **entry 55**, (*RS*)-2-(aminomethyl)propanoic acid hydrochloride, 28267-25-6; **entry 56**, (3*S*,7a*R*)-3-isopropyl-7a-methyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one, 98203-44-2.

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Keywords: 2-pyridone • 2-hydroxypyrimidine • deteurated aminoacids • β-aminoacids • δ-aminoacids

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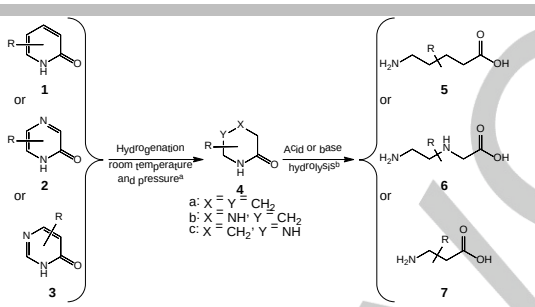

*Preparation of α-, β-, γ- or δ-aminoacids

Key Topic*

Dr. Boulos Zacharie, Dr. Shaun D. Abbott, Christopher B. Baigent, Christopher Doyle and Dr. Ravi Shekar Yalagala*

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An efficient two-step preparation of α-, β-, γ- or δ-aminoacids from 2-hydroxy pyrazines, pyrimidines or pyridines respectively

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